EXTENDED REPORT

Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors

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Objectives: To assess the risk of lymphoproliferative disease or other malignancy (standardised incidence ratios (SIRs)), in patients with primary Sjögren's syndrome according to the American-European Consensus Criteria (AECC), compared with patients with sicca syndrome (non-AECC) and the background population. To identify predictors of malignancy and describe lymphoma types and survival probabilities.
Methods: A linked register study using information from the Malmö Primary SS Register, Swedish Cancer Register, and Cause-of-Death Register for calculation of SIRs was carried out. Detected lymphomas were reclassified according to the WHO classification. Cox regression analysis was used to study the predictive value of clinical, laboratory, and histological findings at the time of diagnosis.
Results: 507 patients with a median follow up of 8 years (range 1 month to 19 years) were included. SIRs (95% confidence interval (CI)) for malignancies in total and for non-Hodgkin's lymphomas (NHL) were 1.42 (0.98 to 2.00) and 15.57 (7.77 to 27.85), respectively, in those fulfilling the AECC (n = 286). In non-AECC sicca patients (n = 221) SIR for malignancy of any kind was 0.77 (0.41 to 1.32); no lymphoproliferative neoplasms were detected. Significant predictors of lymphoproliferative disease were purpura/skin vasculitis (hazard ratio (HR) = 4.64, 95% CI 1.13 to 16.45), low complement factor C3 (HR = 6.18, 95% CI 1.57 to 24.22), low C4 (HR = 9.49, 95% CI 1.94 to 46.54), CD4+ T lymphocytopenia (HR = 8.14, 95% CI 2.10 to 31.53), and a low CD4+/CD8+ T cell ratio $\leqslant$0.8 (HR = 10.92, 95% CI 2.80 to 41.83). 7/12 (58%) NHLs were diffuse large B cell lymphomas.
Conclusion: A 16-fold increased risk for development of NHL was found. CD4+ T lymphocytopenia is an additional strong risk factor for developing lymphoma.

Primary Sjögren's syndrome (pSS) is an autoimmune connective tissue disease with an estimated prevalence of 0.5% among adults, when classified according to the American-European Consensus Criteria (AECC).[1–3] The aetiology is unclear. Genetic, hormonal, environmental (mainly infectious), and other factors (such as birth weight[4]) interact in its pathogenesis.[5 6]

Patients with pSS experience mouth and/or eye dryness as the main consequence of an autoimmune destruction or functional blockade of the exocrine gland tissue. The most frightening complication of pSS is lymphoproliferative malignancy. In 142 patients with SS admitted to the National Institute of Health between 1954 and 1975, seven lymphomas were observed and resulted in a relative risk of lymphoma of 44.4 for pSS.[7] Several studies have confirmed this association and a lifetime risk of around 5%–10%.[8–11] Malignant lymphoma is the only cause of death for which patients with pSS are at increased risk.[11 12] Several predictors of lymphoma development have been identified. Clinical signs such as lymphadenopathy,[10 11 13] swollen salivary glands,[7 10 11 13] palpable purpura or skin vasculitis,[11 14] peripheral nerve involvement,[14] leg ulcers,[13] low grade fever,[14] use of cytotoxic drugs,[7] younger onset pSS,[7 9] and laboratory predictors such as anaemia,[14] lymphopenia,[14] low levels of C3[12 15] and C4,[11 12 15] and cryoglobulinaemia[15 16] have been described. Reports from our group[17 18] and others[19–21] have drawn attention to the high prevalence of CD4+ T lymphocytopenia and its possible connection to lymphoma development.

Since 1976[7] no studies have contributed with prospectively followed cohorts, high precision of assessment of the associated malignancies, and comparison with solid, reliable background population data.

After Kassan's original description,[7] risks of non-haematological malignancies have only been analysed in patient populations identified by hospital discharge registries,[9 22] which are likely to be biased towards patients with more severe pSS.

Lymphoma (and malignancy) incidence and prevalence in the background population are subject to continuous change,[23 24] attributable to population dynamics, true changes in standardised incidence ratios (SIRs), improved diagnosis and survival rates. Risks in the target cohort must be carefully calculated and compared with age, sex and calendar period adjusted expected risks. Swedish Health Registers, including the Cancer Register[25 26] and Cause-of-Death Register,[27] allow a reliable comparison to be made by linking patient registers to official registers using the Swedish personal identification number.[28]

This study aimed at analysing the degree of risk of lymphoproliferative malignancy in a prospectively collected pSS cohort from one centre, identified in an outpatient clinic, taking advantage of the Swedish health system registers, which allow exact detection of incident cases of malignancies.[25] Primary objectives were calculation of SIRs for lymphomas and other malignancies and detection of predictors of lymphoma.

Abbreviations: AECC, American-European Consensus Criteria, ANA, antinuclear antibody; CI, confidence interval; DLBC, diffuse large B cell; HR, hazards ratio; NHL, non-Hodgkin's lymphoma; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; RF, rheumatoid factor; SIR, standardised incidence ratio

Table 1 Baseline patient and disease characteristics

Characteristics	AECC SS without malignancy (n = 253)	Available data (n)	AECC SS + lymphoma/ myeloma (n = 12)	Available data (n)	AECC SS + other malignancy (n = 21)	Available data (n)
Female/male	232/21	253	10/2	12	19/2	21
Age at diagnosis (years), median (range)	56 (16–82)	254	58 (25–75)	12	66 (40–80)	21
Biopsy positive†, No (% of available)	213 (89)	240	10 (100)	10	18 (86)	21
SSA/B positive, No (% of available)	143 (57)	250	10 (83)	12	12 (48)	21
RF positive, No (% of available)	139 (58)	241	9 (75)	12	9 (40)	20
ANA positive, No (% of available)	212 (84)	251	12 (100)	12	16 (76)	21
Salivary gland swelling, No (% of available)	74 (31)	242	5 (42)	12	2 (10)	21
Purpura or skin vasculitis, No (% of available)	25 (10)	240	4 (33)*	12	0 (0)	21
IgG (g/l), median (range)	1 16.2 (1.0–92.0)	240	15.2 (8.2–36.0)	12	15.5 (5.4–33.9)	21
C3 (g/l), median (range)	0.97 (0.17–1.73)	207	0.78 (0.50–1.01)**	11	1.1 (0.70–1.46)	20
C4 (g/l), median (range)	0.23 (0.02–1.60)	207	0.16 (0.01–0.37)	11	0.29 (0.1–0.75)	20
CD4+ (%), median (range)‡	45 (4–75)	142	35 (12–54)**	11	40 (12–47)	12
CD8+ (%), median (range)‡	25 (3–65)	142	44 (22–68)***	11	28 (14–79)	12
CD4/CD8, median (range)	1.7 (0.3–8.1)	142	0.7 (0.2–2.3)**	11	1.4 (0.2–3.3)	12
CD4-penia, No (% of available)§	24 (17)	142	8 (73)***	11	3 (25)	12

Significantly different from AECC SS without malignancy with *$p<0.05$; **$p<0.01$; ***$p<0.001$.
†Biopsy positive: lower lip salivary gland biopsy with a focus score >1; ‡percentage of total lymphocyte count; §CD4-penia defined as either CD4+ T cells <300 cells/μl or CD4+ T cells <30% of total lymphocyte count or CD4/CD8 ratio <0.8.

PATIENTS AND METHODS

Malmö Sjögren's syndrome register

Since 1984 patients with pSS have been consecutively registered and followed up prospectively at intervals of 6 months to 2 years and clinical, laboratory, and histological data have been collected.

Swedish healthcare registers

Nationwide population based mandatory registers for census data, death, and cancer incidence, identifying subjects according to the unique national identification number,[28] allow for linkage of these registers with each other and local registers such as the Malmö SS Register. The coverage (99%) and quality of information has been found to be excellent.[25 29]

Study cohort and observation time

The study cohort consisted of all 507 patients included in the pSS register up to December 2002, who lived in Sweden and fulfilled either the Copenhagen,[30] the 1993 European[31] or the American-European Consensus Criteria (AECC)[1] (n = 286) for pSS. None of the patients had known hepatitis C, HIV, sarcoidosis or pre-existing lymphoma. Observation covered the time from 1984 until 31 December 2002, a period for which information from the National Death and Cancer Register was available. Thus the individual observation time was from the time point of diagnosing pSS until the first malignancy, death or the closure date of 31 December 2002, whichever occurred first. Four AECC and six non-AECC patients could not be matched with the national registries, thus being lost to follow up. The individual observation time was a median of 8 years (1 month to 19 years). The total observation time was 2464 years in AECC SS and 1840 in the non-AECC sicca patients.

Representativeness of the study cohort

Most of the patients lived in Malmö and surroundings. Our cohort covers about 20% to 30% of those expected to fulfil the AECC in our region, including those with subclinical disease.[12]

Verification of lymphoma types

The type of the lymphoproliferative malignancies was reclassified according to the 2001 WHO classification for Tumours of Haematopoietic and Lymphoid Tissues[32] by one of the authors (OL).

Variables in the predictor analysis (only AECC group, n = 286)

As possible predictor variables for lymphoma development we included salivary gland swelling, purpura or skin vasculitis, autoantibodies (antinuclear antibodies (ANA), anti-SSA/Ro, anti-SSB/La, IgM rheumatoid factor (RF)), salivary gland biopsy, serum immunoglobulins, levels of complement factors C3 and C4, and lymphocyte subtype abnormalities, especially absolute or relative CD4+ T lymphocytopenia or a low ratio of CD4+/CD8+ T cells. Normal ranges: IgG: 6.19–14.9 g/l, IgA: 0.7–3.65 g/l, IgM: 0.39–2.08 g/l, C3: 0.77–1.38 g/l, C4: 0.12–0.33 g/l, CD4+%: 30–50% of lymphocytes, CD4+ absolute count: 300–2000 cells/μl, CD4+/CD8+ ratio: 0.8–3.0. Determination of peripheral blood lymphocyte subtype distribution had been performed by flow cytometry, beginning 1988, as described,[17 33] in 165/286 (58%) AECC patients. CD4+ T lymphocytopenia was defined according to the reference limits of our laboratory. Patients with severe CD4+ T lymphocytopenia were tested repeatedly to ensure the reliability of the results and investigated for predisposing conditions. Only CD4+ T lymphocytopenia without evidence for drug induction or virus infection was included in the statistical calculations. Cryoglobulins were not analysed routinely, because cryoglobulinaemia has been shown to be unusual in Nordic populations.[34]

Linkage procedure

The national personal identification number, issued to all permanent residents in Sweden, was used and the SS register was linked to the National Cancer and Cause-of-Death Registers by the National Board of Health and Welfare, retrieving all cancer diagnoses, deaths, and causes of death in the study population until 31 December 2002.

Statistics

Calculation of SIRs

Expected risks for malignancies were calculated by comparison with the background population (region of Southern Sweden) matched for age, sex, and calendar period. An SIR was calculated by dividing the observed by the expected risk. Exact 95% confidence intervals calculated from binomial distributions were created for the SIRs.

Cancer diagnoses were grouped (for details see table 2) according to *International Classification of Diseases*, 7th Revision

Table 2 SIRs and 95% CI for selected types of malignancies, detected after the diagnosis of SS

	ICD7	Observed (n)	Expected (n)	SIR	95% CI
AECC Sjögren's syndrome (n = 286), years at risk 2464					
All malignancies		**33**	**23.21**	**1.42**	**0.98 to 2.00**
NHL	**200, 202**	**11**	**0.71**	**15.57**	**7.77 to 27.85**
Myeloma	203	1	0.31	3.27	0.08 to 18.23
Mb Hodgkin	201	0	0.05		
Leukaemia	201, 2041–208	0	0.45		
Mouth and throat	140–48	1	0.33	3.03	0.08 to 16.88
Gastrointestinal	150–157	8	4.56	1.75	0.76 to 3.46
Lung	1620–1622	4	1.48	2.71	0.74 to 6.94
Breast	170	3	5.93	0.51	0.10 to 1.48
Female reproductive system	171–176	0	2.90		
Prostate/testis	177–178	0	0.72		
Kidneys/urinary tract	180 to 181	1	1.30	0.77	0.02 to 4.29
Skin/non-melanoma	190	2	1.03	1.93	0.23 to 6.98
Skin/melanoma	191	0	0.87		
Brain	193	0	0.64		
Thyroid gland	194	1	0.15	6.86	0.17 to 38.21
Connective tissue	196–197	1	0.14	7.14	0.18 to 39.80
Non-AECC sicca syndrome (n = 221), years at risk 1840					
All malignancies		**13**	**16.89**	**0.77**	**0.41 to 1.32**
NHL	**200, 202**	**0**	**0.56**		
Myeloma	203	0	0.24		
Mb Hodgkin	201	0	0.03		

(ICD7). Risk estimates were calculated for the first malignancy after the pSS diagnosis without latency period.

Predictor analysis

Cox regression analysis with proportional hazards assumption adjusted for age was applied to study the influence of laboratory, clinical, and histological findings at the time of diagnosis on lymphoma incidence. For CD4+ T lymphocytopenia, the observation time from the first available flow cytometry (in all cases before lymphoma development) until lymphoma or cancelling date was used. The small number of lymphoproliferative malignancies (12 patients) did not allow multivariate analysis to be used. The high prevalence of a positive salivary gland biopsy both in patients without (90%) and those with (100%) lymphoma makes this variable unsuitable as a predictor. Predictors were used as continuous variables whenever possible, expressing hazard ratios (HRs) as risks for one standard deviation change. For complement and immunoglobulins, partly owing to U shaped distributions of the risk estimates, the results were divided into quartiles, comparing highest and lowest quartiles with the two in between.

Power analysis

With the available patient number and the number of non-Hodgkin's lymphomas (NHLs) in comparison with the number expected our study had an 80% power of detecting a statistically significant increase of the risk of lymphoma by 500% to an SIR of 5.1, within the patient group fulfilling the AECC. The detected SIR and its 95% confidence interval (CI) are above this level.

RESULTS

Demographic and basic clinical variables

Ninety two per cent of the patients were Scandinavian, 90% were women. The disease duration from appearance of the first symptom until diagnosis (estimated by the patient at the first contact) was a median of 7 years. Table 1 gives baseline characteristics by patient group.

Standardised incidence ratios (SIRs) for lymphomas and solid tumours

In the AECC group 33 tumours were detected during the 2464 years of observation, while 23.21 were expected, resulting in an SIR of 1.42 (95% CI 0.98 to 2.00). Two of these patients had had other malignancies before the diagnosis of pSS. Furthermore, before their pSS diagnosis 11 patients had had diagnosed malignancies, including a chronic myeloid leukaemia, but did not develop malignancies later on. After the pSS diagnosis two patients developed more than one malignancy: one patient developed a myeloma after a lymphoma, one patient renal cancer after a breast cancer. At least four patients later developing lymphoproliferative neoplasms had had skin cancers previously (two cases of basal cell cancers, one squamous cell cancer, and in the fourth a combination of both types), detected by rereading the lymphoma patients' case records (reporting of basal cell carcinomas was not mandatory before 2003). For non-AECC patients the SIR for all cancers was 0.77 (0.41 to 1.32) no lymphoproliferative diseases were observed after pSS diagnosis.

In 286 AECC patients with a median observation time of 7 years, 11 NHLs, and one myeloma occurred as first malignancy after pSS diagnosis. The expected number for NHL was 0.71, resulting in a SIR of 15.57 (95% CI 7.77 to 27.85, $p<0.0001$). The patient registered as myeloma in the cancer register had simultaneously a diffuse large B cell (DLBC) lymphoma according to several re-evaluations.

Table 2 gives the SIRs for selected malignancies. To summarise, patients with pSS according to AECC have a non-significant increase in total risk of malignancy (point estimate 1.42). There was an excess of 10.2 malignancies, completely attributable to the excess in lymphoma/myeloma. This results in an excess malignancy of 4.2 per 1000 patient years at risk. The risk of lymphoma increased with time after the diagnosis of pSS: during the first 5 years the SIR for NHL was 6.4 (95% CI 1.3 to 18.7), during years 6–10 it was 11.1 (3.0 to 28.5), and during years 10–15 it was 20.8 (6.8 to 48.6). The shortest duration between diagnosing pSS and lymphoma was 10 months in a patient with a 10 year history of

Table 3 Clinical, laboratory, and histological features of patients developing lymphoproliferative neoplasms

	Patient No											
Characteristics	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Age at pSS diagnosis	75	52	69	54	67	66	59	50	52	53	25	57
Age at lymphoma/ myeloma onset	76	58 61	72	61	78	73	71	57	65	59	33	67
Death/age at death	+ 82	+ 62	−	−	+ 79	+ 74	−	+ 57	−	+ 61	+ 39	−
Symptom duration before pSS diagnosis	10	16	21	12	18	0	6	18	25	11	2	4
Sex	Female	Male	Male	Female	Female	Female	Female	Female	Female	Female	Female	Female
Lymphoma type (WHO)	Small lymphocytic B cell/chronic lymphatic leukaemia	Small lymphocytic B cell+ Myeloma	Follicular B cell	Small lymphocytic B cell = Waldenström MG	Diffuse large B cell	Diffuse large B cell	Diffuse large B cell**	Anaplastic large T cell	Diffuse large B cell	Diffuse large B cell	Diffuse large B cell	Myeloma + diffuse large B cell
Grade	Low	Low	Low	Low	High	High	High	High	High	High	High	(High)
Primary localisation	BM, LNs	BM, LNs	Salivary glands	BM	LN groin	Right knee hollow	Salivary gland? LNs neck, intra-abdominal, BM	LNs, liver spleen, BM	Lung parenchyma	BM, LNs	Salivary glands, LNs	LNs
Salivary gland swelling	−*	+*	−*	+†	+*	+*	+*	−*	+†	+†	+*	−*
Palpable purpura/skin vasculitis	−*	+*	−*	−*	−*	−*	+*	+*	+†	+†	+*	+†
Peripheral neuropathy	−*	+*	−*	−*	+†	+†	−*	+†	+†	+†	+†	−*
Enlarged LN or spleen	−*	−*	−*	−*	−* +†	−*	−*	+†	+†	+	−*	+*
Concomitant lymphoma predisposing condition	Squamous cell cancer*	Psoriasis†	Psoriasis* *H pylori*† Chronic gastritis	–	Basal cell cancer†	Hashimoto†	*H pylori* Squamous + basal cell cancer†	–	Coeliac disease* *H pylori*† Hashimoto*	–	Sibling with psoriasis	Basal cell cancer†
RF	+*	+*	−*	+*	+†	+*	+*	−*	+*	−	+*	+*
SSA/SSB	−†	+*	+†	+*	+*	+†	−*	+†	+†	+*	+*	+*
ANA	+*	+*	+*	+*	+*	+*	+*	+†	+*	+*	+*	+*
Cryoglobulinaemia	ND	+†	ND	ND	ND	ND	−*	−*	+*	ND	+*	ND
Lymphopenia	−*	−*	−*	−*	−*	+*	+*	+†	+*	−*	+*	−*
Anaemia	−*	−*	−*	−*	−*	+*	−*	−†	+*	−*	+*	−*
C3 (g/l)	0.70*	0.55*	0.98*	0.83*	0.84*	0.75*	0.50*	0.83*	0.78*	1.01*0.81†	0.73*	1.06†
C4 (g/l)	0.36*	0.13*	0.27*	0.29*	0.14*	0.16*	0.01*	0.16*	0.18*	0.37*0.12†	0.06*	0.23†
CD4-penia§	ND	+*	+*	−*	+*	+*	−†	+*	+*	−*	+*	+*
IgG (g/l)	8.2*	14.0*	11.9*	13.8*	16.0*	27.0*	11.3*	23.0*	34.1*	14.4*	36.0*	24.6*
IgA (g/l)	1.72*	2.20*	2.20*	2.14*	2.82*	1.38*	1.29*	1.00*	0.13*	2.30*	3.31*	2.98*
IgM (g/l)	0.63*	2.30*	1.76*	1.54*	0.86*	2.03*	1.11*	1.03*	1.33*	0.40*	1.98*	1.51*
Monoclonality	−*	+* IgG	−*	+† IgM	+† IgM	−*, oligo†	−*	−*	−*	−*	+* IgM	Oligo*
Salivary gland biopsy¶	+*	+*	‡	+*	+*	+*	+*	+*	+*	+*	+*	ND

*Evaluated at diagnosing pSS; †developing during the course of disease before lymphoma development, but not present or not analysed at first visit; ‡biopsy in this case contained insufficient glandular tissue for evaluation. §CD4-penia is defined as number of CD4 <300 cells/μl, % of CD4 <30, or ratio of CD4/CD8 <0.8; ¶+ = focus score >1; **this patient had had a pseudolymphoma in a submandibular gland before her pSS was diagnosed (18 years before the large B cell lymphoma). At re-evaluation of the tissue the lymphoepithelial lesion without full blown malignancy was confirmed.

ND, not done; BM, bone marrow; LN, lymph node.

Table 4 Predictors of lymphoproliferative disease (n = 12) within the AECC group (n = 286)

Predictor variable	Total AECC cohort (No available)	Lymphoma patients (No available)	HR (95% CI)	p Value
Age at diagnosis	286	12	1.02/yr (0.97 to 1.06)	0.516
Salivary gland swelling (yes/no)	81/194	5/7	2.02 (0.62 to 6.61)	0.247
Purpura/skin vasculitis (yes/no)	29/244	4/4	4.64 (1.13 to 16.45)	0.017
ANA positivity (yes/no)	240/44	12/0	–	
RF positivity (yes/no)	156/117	9/3	3.03 (0.80 to 11.24)	0.102
SSA/SSB (yes/no)	163/120	10/2	2.58 (0.69 to 9.63)	0.159
CD4-penia (yes/no)	35/130	8/3	8.14 (2.10 to 31.53)	0.002
CD4+ (%)*	165	11	0.57 (0.34 to 0.93)	0.026
CD8+ (%)*	165	11	1.76 (1.14 to 2.73)	0.011
CD4+/CD8+ratio*	165	11	0.23 (0.07 to 0.73)	0.013
CD4+/CD8+ratio ⩽ 0.8 (yes/no)	29/136	8/3	10.92 (2.8 to 41.83)	0.000
C3 ⩽0.83 g/l†	60	8	6.18 (1.57 to 24.22)	0.009
C3 = 0.84–1.12 g/l†	118	3	1.0 (referent)	
C3 ⩾1.13 g/l†	60	0	–	–
C4 ⩽0.18 g/l†	62	7	9.49 (1.94 to 46.54)	0.006
C4 = 0.19–0.30 g/l†	116	2	1 (referent)	
C4 ⩾0.31 g/l†	60	2	1.60 (0.22 to 11.42)	0.641
IgG ⩽12.0 g/l†	71	3	1.41 (0.31 to 6.32)	0.65
IgG = 12.1–21.4 g/l†	133	5	1 (referent)	
IgG ⩾21.5 g/l †	68	5	2.54 (0.67 to 9.65)	0.17

The analysis was performed using Cox regression with adjustment for age. *HR for one standard deviation (SD) increase. CD4+ (%) mean (SD) 43.32 (12.20), CD8+ (%) mean (SD) 28.59 (13.01), CD4+/CD8+ratio mean (SD)1.90 (1.18). †Owing to a U-shaped distribution for the risk of lymphoma, quartiles for C3, C4, and IgG were used, testing the risks for the highest and lowest quartiles versus the two middle ones. For all predictors the first ever assessment is used.

sicca symptoms before pSS diagnosis. The point estimate for risk of pulmonary carcinomas was increased, although the small number makes precision poor: SIR 2.47 (0.67 to 6.32). The SIR for all non-haematological malignancies in the AECC patients with SS was 0.93 (0.59 to 1.40).

Lymphoma types after re-evaluation

Table 3 gives details of the 12 cases with reclassification of the WHO histopathology of the lymphoma biopsies. Eleven of 12 patients had B cell NHLs (two of them appearing simultaneously with or followed by a myeloma). One patient had a T cell lymphoma. Seven of the 11 B cell lymphomas were DLBC lymphomas. This type comprised 58% of all NHLs in our cohort. Only two lymphomas (a follicular and a DLBC) were localised to the salivary gland region, but both were interpreted as originating from lymph nodes, in one case within and in the other adjacent to the parotid gland. In one patient with high grade DLBC lymphoma, transformation from a MALT lymphoma could not be excluded. One patient had had a submandibular pseudolymphoma 18 years before the DLBC lymphoma in a neck lymph gland. Re-evaluation of the tissue from this submandibular gland only disclosed a lymphoepithelial lesion.

Survival after lymphoma diagnosis

Seven of 12 patients with lymphoma/myeloma had died (table 3). The median survival time for all lymphoma patients was 43 months (low grade 76, high grade 31, log rank test 0.08).

Predictors of lymphoma development: Cox regression analysis within the AECC group (n = 286) (table 4)

The strongest predictor of lymphoma was a lowered CD4+/CD8+ T cell ratio. Eight of 11 patients with available lymphocyte subtyping had a CD4+/CD8+ T cell ratio of ⩽0.8, resulting in an HR of 10.92 (95% CI 2.80 to 41.83). The small number of events made multivariate regression analysis impossible, only adjustment for age was performed.

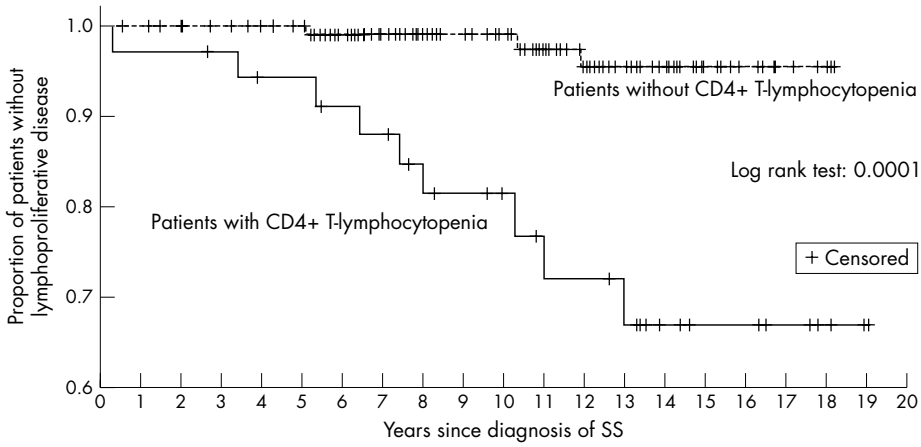

Figure 1 Kaplan-Meier plots for the risk of lymphoproliferative disease in patients with or without CD4+ T lymphocytopenia.

Levels of immunoglobulins were not significantly associated with increased risks. Patients later developing lymphoma/myeloma had significantly lower relative numbers of CD4+ T lymphocytes, increased CD8+ T lymphocytes, and a lowered ratio of CD4+/CD8+ ($p<0.01$, <0.001, and <0.01 respectively) (table 4). Figure 1 shows Kaplan-Meier plots for the risk of developing NHL/myeloma in patients presenting with or without CD4+ T lymphocytopenia. The time between the lymphocyte count and the lymphoma was a median of 88 months (4–156). Low levels of complement factors C3 and C4 predicted haematological malignancy. Nine of the 12 patients had disorders associated with lymphoma development itself, such as coeliac disease,[35] *Helicobacter pylori*,[36] psoriasis,[37] autoimmune thyroiditis,[38] skin cancers.[39 40] Methotrexate, auranofin, ocular (topical) ciclosporin, and chloroquine were the only antirheumatic drugs used before lymphoma appearance (table 3).

DISCUSSION

We have performed an analysis of the risk of malignancy, in general, and lymphoproliferative neoplasms, in particular, in our prospectively followed cohort of patients with pSS. The focus of this study was on patients fulfilling the AECC for pSS.[1]

There are two main new messages:

- The often cited risk estimate for NHL of a 44-fold increase compared with the background population is probably valid only for highly selected patient populations with severe disease, while a lower risk estimate as found in this study (16-fold increase) is probably more representative for an average pSS population. No other malignancies were overrepresented with statistical significance, although the power to detect such deviations was low.
- Our results show a substantially increased risk for developing lymphoproliferative malignancy in patients with a decreased CD4+/CD8+ T lymphocyte ratio. No previous longitudinal cohort study has evaluated the significance of T cell disturbances with respect to outcome in pSS, even though the presence of CD4+ T lymphocytopenia was described years ago and suggested to be associated with cases of NHL.[17] Earlier proposed risk factors such as hypocomplementaemia and skin vasculitis are confirmed.

Additional interesting observations include the presence of further predisposing factors, such as autoimmune thyroiditis, coeliac disease, *H pylori* infection, skin cancers or psoriasis, which may deserve increased awareness and intensified search for lymphoma when combined with suspicious clinical or laboratory signs. The significance of these coincidences requires confirmation. However, the high prevalence of earlier non-melanoma skin cancers in our lymphoma patients is in concordance with several recent reports on increased lymphoma risks in patients with skin cancer.[39 40] Surprisingly, the NHLs in our pSS cohort are high grade, diffuse large B cell (DLBC) lymphomas in 58% of cases.

In concordance with our previous study on mortality, the present investigation also underlines the importance of strict and universally accepted classification criteria, as patients not fulfilling the AECC criteria do not show any increased lymphoma risk, in contrast with those who do fulfil the criteria.

The strengths of the present study are the strict prospective design of the data collection from one centre, in combination with the highly reliable Swedish general health registers.[25] In addition, the follow up time of up to 19 years (median 8 years) is relatively long. This seems to be a prerequisite to allow evaluation of long term severe outcomes such as death or cancer development. When Kirtava *et al* in 1995 described six patients with CD4+ T lymphocytopenia from our department (follow up for up to 7 years), only one had developed lymphoma[17]. In the present study we found that another two of these patients had developed a lymphoma. The mean time between diagnosing pSS and the appearance of the lymphoma was in the present study 8 years (1–13 years). The risk of lymphoma increases with time, exemplified by the highest SIR of >20 being observed in those followed up for more than 10 years.

CD4+ T lymphocytopenia has been described in association with, and pre-existing before, NHLs.[41–44] In our study all the risk calculations were performed using the first available CD4+ T cell analysis, most often performed at or shortly after the time of diagnosing pSS, and always before the lymphoma detection (table 3), which excludes the possibility of a lymphoma-induced CD4+ T lymphocytopenia. We have to acknowledge the lack of systematic cryoglobulin analysis in our cohort as an important drawback. The assumption that cryoglobulinaemia is rare in Swedish patients with pSS[34] needs to be revised in the light of the new classification criteria.

Our study differs from previous studies in several important aspects. The lymphoma incidence was lower than in Kassan's original description, which, however, as the authors themselves point out, may not be generalised to other populations less prone to selection bias.[7] Furthermore, their study had slightly less precision, being based on only seven (four pSS lymphoma) cases. The described histiocytic diffuse and Lennert's lymphomas in six of seven cases would correspond to high grade DLBC and T cell lymphomas in the present WHO classification. This is in accordance with our cases with predominantly high grade DLBC lymphoma. In contrast, two other case series have documented a predominance of low grade lymphomas, quite often in salivary glands and of MALT type,[10 45] while another study did not find any MALT lymphomas among four patients with SS and associated NHLs.[8] Only one of our cases could possibly be classified as MALT lymphoma. Our approach with linkage to the validated national cancer register excludes any major detection bias, which may operate when cases are identified in routine clinical settings. Transformation from earlier MALT lymphoma into DLBC lymphoma can, however, not be excluded. Survival after lymphoma was comparable with previous reports when groups of high and low grade lymphomas were compared separately.[10]

The lymphoma types found in our study are similar to those found in Swedish RA cohorts.[46] Also in systemic lupus erythematosus, the associated lymphomas are predominantly of the DLBC type.[47] The reported increase in risk with disease duration is similar to studies in rheumatoid arthritis (RA), but in contrast to studies in systemic lupus erythematosus, where the highest risk is observed within the first 5 years after diagnosis.[47] In RA high disease activity is the most important predictive factor for lymphoma.[48] Disease activity is difficult to assess in pSS. Correlation between extraglandular disease and CD4+ T lymphocytopenia due to apoptosis was described in pSS.[19] It seems conceivable that a longstanding deficiency in immune surveillance finally allows malignant transformation in antigen stimulated proliferating B cells.

The causes of CD4+ T lymphocyte depletion or disturbed balance between CD4+ and CD8+ T cells are unknown. Anti-CD4+ antibodies have been documented in patients with pSS without correlation to the level of CD4+ T cells.[49] Virus infections are typical causes of lymphopenia, and HIV infection is the prototype of virus-induced CD4+ T lymphocytopenia, associated with lymphoma development.[50] Hepatitis C[51] and Epstein-Barr virus[52] are viruses associated with lymphoma development and autoimmunity. Coxsackie

B virus was recently proposed as an aetiological factor in pSS,[53 54] but its potential to induce cytopenia has not been studied. CD4+ T cells and subsets of the CD4+ T lymphocytes are important in tumour immunity.[55] To what extent the different predictors for lymphoma development, such as cryoglobulinaemia, hypocomplementaemia, B cell activation, and CD4+ T cell depletion have a shared aetiology or represent different aspects of risk needs to be elucidated.

In summary, our results suggest that CD4+ T lymphocytopenia is a useful clinical predictor, which possibly is of crucial importance in the sequence of events leading to lymphoma development in patients with pSS. Previously proposed risk factors, such as hypocomplementaemia and skin vasculitis could be confirmed, while aggressive types of lymphomas were common in our cohort. The overall lymphoma risk was lower than proposed earlier, but increased with disease duration.

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